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Variant connective tissue (joint hypermobility) and dysautonomia are associated with multimorbidity at the intersection between physical and psychological health

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Abstract

The symptoms of joint hypermobility extend beyond articular pain. Hypermobile people commonly experience autonomic symptoms (dysautonomia), and anxiety or related psychological issues. We tested whether dysautonomia might mediate the association between hypermobility and anxiety in adults diagnosed with mental health disorders and/or neurodevelopmental conditions (hereon referred to as patients), by quantifying joint hypermobility and symptoms of autonomic dysfunction. Prevalence of generalized joint laxity (hypermobility) in 377 individuals with diagnoses of mental health disorders and/or neurodevelopmental conditions was compared to prevalence recorded in the general population. Autonomic symptom burden was compared between hypermobile and non-hypermobile patients. Mediation analysis explored relationships between hypermobility, autonomic dysfunction, and anxiety. Patient participants had elevated prevalence of generalized joint laxity (38%) compared to the general population rate of 19% (odds ratio: 2.54 [95% confidence interval: 2.05, 3.16]). Hypermobile participants reported significantly more autonomic symptoms. Symptoms of orthostatic intolerance mediated the relationship between hypermobility and diagnosis of an anxiety disorder. Patients with mental health disorders and/or neurodevelopmental conditions have high rates of joint hypermobility. Accompanying autonomic dysfunction mediates the association between joint hypermobility and clinical anxiety status. Increased recognition of this association can enhance mechanistic understanding and improve the management of multimorbidity expressed in physical symptoms and mental health difficulties.

KEYWORDS
anxiety, autonomic dysfunction, joint hypermobility, multimorbidity

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1 | INTRODUCTION

Joint hypermobility refers to the capacity for a joint to move beyond what are considered normal limits (Baeza-Velasco, Sinibaldi, & Castori, 2018) as a result of ligamentous laxity (Clinch et al., 2011; Sobey, 2015) and is a representation of variant connective tissue, including collagen and other structural elements of the extracellular matrix. Generalized joint hypermobility is commonly assessed using the Beighton Scale, which quantifies hypermobility across specific joints (fifth finger metacarpal-phalangeal joints, wrists, knees, elbows, and spine) Beighton, Solomon, & Soskolne, 1973; Junge et al., 2019). For the purpose of this study, generalized joint laxity (GJL) is inferred if an individual achieves a Beighton score of 4 or more (i.e., increase range of movement in 4 of 9 joints tested). The prevalence of GJL is estimated between 11 and 30% of the population and is predominantly manifested in those assigned female at birth (Junge et al., 2019; Juul-Kristensen et al., 2017; Mulvey et al., 2013). Also, there are reported differences between ethnicities on the prevalence of GJL (e.g., higher prevalence in African and Asian populations [Hakim, Malfait, & De Paepe, 2010; Reuter & Fichthorn, 2019] compared to European populations). GJL is often associated with musculoskeletal symptoms, particularly pain (Clinch et al., 2011; Sobey, 2015), where hypermobility spectrum disorder (HSD) or hypermobile Ehlers–Danlos Syndrome (hEDS) may be diagnosed (hereon *symptomatic* hypermobility), replacing the former constructs of joint hypermobility syndrome and EDS-III/HT. The prevalence of symptomatic hypermobility in general practice (community physician) settings in the United Kingdom is reported as 194.2 per 100,000 people but the condition is thought to be under-diagnosed and the prevalence of HSD and hEDS are suspected to be much higher than initially thought (Demmler et al., 2019). To our knowledge, further population-level data on the prevalence of diagnosed symptomatic hypermobility conditions are not available; however, GJL prevalence data exist (Clinch et al., 2011; Mulvey et al., 2013). From the available data, GJL and clinically significant symptomatic hypermobility seem to occur at high rates across populations, carrying major health costs implications, which may not yet be fully quantified or recognized due to high rates of under/misdiagnosis and co-occurring impact on both mental and physical health.

In addition to pain, musculoskeletal, and skin-related symptoms (Demmler et al., 2019), strong associations are observed between hypermobility and autonomic dysfunction (Hakim et al., 2017). Autonomic dysfunction impairs automatic physiological regulation across bodily systems affecting heart rate and blood pressure, respiration, digestion, urination, defecation, metabolism, the production of bodily fluids (including sweat, saliva, and tears), and the control of body temperature (Hakim et al., 2017; Smith, 2017). Within the hypermobility literature, most attention is paid to cardiovascular autonomic dysfunction: Up to 80% of people with hypermobility experience orthostatic intolerance (including postural tachycardia (Mathias et al., 2011; Wells et al., 2018) and postural hypotension, characterized by symptoms such as light-headedness when standing upright (Celletti et al., 2017; Chan, Krahe, Lee, & Nicholson, 2019; Stewart, 2013), and autonomic neurally mediated syncope. Postural tachycardia syndrome (PoTS) may be diagnosed when objective physiological criteria provide an explanatory account for orthostatic intolerance, and there is a phenomenological overlap between anxiety symptoms and those of orthostatic intolerance. Hence, the (common) concurrence of hypermobility and orthostatic intolerance represents an expression of multimorbidity (the presence of two or more long-term health conditions [National Institute for Health and Care Excellence, 2018]). There is a need to recognize the impact of multimorbidity and rethink the prevailing divisions in clinical medicine, education, and treatment guidelines that are frequently based on single systems, especially given the interaction between physical and mental health problems makes each harder to treat (Whitty et al., 2020).

There is also growing recognition of associations between hypermobility and other non-cardiovascular autonomic symptomatology. These include: gastrointestinal disorders including irritable bowel syndrome (Fikree, Chelimsky, Collins, Kovacic, & Aziz, 2017), bladder dysfunction (De Wandele et al., 2014), hyperhidrosis (excessive sweating indicating sudomotor dysregulation) (Castori, 2012; De Wandele et al., 2014) and secretomotor symptoms (including dry mouth or dry eyes) (Kumar & Lenert, 2017; Wang, Fealey, Gehrking, & Low, 2008). These symptoms add to the burden on quality of life (Fikree et al., 2017; Hakim et al., 2017). Together, the combination of autonomic dysfunction with chronic pain has a multi-systemic and detrimental impact on the lives of hypermobile people (Bulbena et al., 2017).

Further multimorbidity arises through a complex association between hypermobility and vulnerabilities to mental health disorders and/or the presence of neurodevelopmental conditions. A consistent and common observation is that compared to non-hypermobile individuals, people with hypermobility are significantly more likely to experience symptomatic anxiety (Bulbena et al., 2011; Bulbena et al., 2017; Smith et al., 2014). Similarly, it has also been shown that people with hypermobility have a higher probability of experiencing depression (Smith et al., 2014) or bipolar disorder (Cederlöf et al., 2016). There is also growing evidence that hypermobility is more common among autistic people and those with attention deficit hyperactivity disorder (Cederlöf et al., 2016) and Tourette syndrome (Csecs et al., 2020). Preliminary evidence in a small sample suggests hypermobility is more common in people with anorexia nervosa (Goh, Olver, Huang, Millard, & O'Callaghan, 2013). It may well be that these conditions have commonality in shared biological mechanisms including dysautonomia. While we may not yet have a comprehensive mechanistic understanding of why hypermobility is more prevalent in people with mental health and/or neurodevelopmental conditions compared to the general population, the recognition of such associations represents an important step towards implementing joined-up therapeutic approaches to manage multimorbidity and reduced quality of life, reduced life expectancy, and increased functional difficulties inherent in the experience of two or more long-term health conditions (National Institute for Health and Care Excellence, 2018).

Despite the aforementioned relationships, to our knowledge, there has been no direct characterization within those with mental

health conditions with regards to autonomic dysfunction and its links to hypermobility in people. Such characterization is needed to map the associated burden on quality of life (Fikree et al., 2017; Hakim et al., 2017) and guide clinical services in the provision of more effective, holistic, and targeted interventions for patients with interacting challenges to psychological and physical health (Bulbena et al., 2017). Chronic and severe psychiatric disorders increase the likelihood of physical health problems (including cardiovascular disease, respiratory disease, and infections) and premature mortality (Liu et al., 2017; Osborn, 2001). Correspondingly, if autonomic dysfunction can be shown to have a mediating relationship in people with hypermobility and mental health conditions, individually focused interventions to improve autonomic function may help alleviate many of the enmeshed psychological and physical symptoms experienced by hypermobile individuals (Davies et al., 2021; Eccles & Davies, 2021).

In some forms of PoTS, heart rate acceleration is thought to compensate for dysfunctional vasoconstriction and may give rise to physiological symptoms (e.g., palpitations and light-headedness) that are shared with panic and anxiety states (Eccles, Owens, Mathias, Umeda, & Critchley, 2015). Coupled with differences in interoception and brain structure and function (e.g., amygdala and insular cortex) associated with hypermobility (Eccles et al., 2012; Mallorqui-Bague et al., 2014), such deregulated responses are likely to affect neural processes supporting emotional feelings (Critchley, 2009; Seth, Suzuki, & Critchley, 2011).

The aim of this study is to quantify the frequency of GJL and autonomic dysfunction in those with diagnosed mental health disorders and/or neurodevelopmental conditions. We hypothesized that people with diagnosed mental health disorders and/or neurodevelopmental conditions will have higher rates of GJL compared to a large population cohort study (prevalence of GJL in adolescence in the Avon Longitudinal Study of Parents and Children [ALSPAC] cohort [Clinch et al., 2011]). We will use these data because this cohort represents the most robust indication of prevalence of GJL in the general population so far and is similar to the rates found in a large population survey of adults that assessed GJL by self-report (Mulvey et al., 2013). We also hypothesized that hypermobile people with diagnosed mental health disorders and/or neurodevelopmental conditions will be more likely to experience autonomic dysfunction across different organ systems compared to participants who are not hypermobile. Since hypermobility is more common in those assigned female at birth, we also proposed that more assigned female at birth than assigned male individuals in our study would have GJL and would experience more autonomic symptoms. We also postulated that symptoms of autonomic dysfunction, specifically orthostatic intolerance, would mediate the relationship between hypermobility and anxiety status.

2 | MATERIALS AND METHODS

2.1 | Participants and ethical considerations

The study enrolled a total of 377 participants from community mental health centers and specialist mental health centers in Sussex with appropriate ethical approvals (NRES Ethics Committee [South East Coast] [12.LO.1942]). Full informed consent was obtained and the study was conducted according to the standards of the Declaration of Helsinki. Data for the comparison group were derived from the ALSPAC birth cohort study (Clinch et al., 2011) where the Beighton score was available for 6,022 adolescents from the general population. While these data were collected in adolescents, the levels of GJL in this sample are comparable to that shown in adults (18% of the population) (Mulvey et al., 2013).

2.2 | Measures and materials

The Autonomic Questionnaire and Quality of Life Score (AQQoL) is a self-report questionnaire that measures symptoms of autonomic dysfunction (Iodice, 2013). It includes subscales of symptoms related to: orthostatic intolerance (items 1–9), gastrointestinal (items 10–13), bladder (items 14–15), secretomotor (items 16–18), sudomotor (items 19–21), and sleep (items 41–45). Participants were asked to rate how often they experienced symptoms of autonomic dysfunction on a 5-point Likert scale (from "no" to "yes – daily"), for example, "do you feel dizzy or lightheaded?". Within the AQQol, musculoskeletal symptoms (predominately pain—items 27–40) were also surveyed (e.g., "do you have any of the following symptoms? a) pains in the knees b) pains in the fingers"). Participants were asked to rate these questions on a 3-point Likert scale in relation to frequency (from "no" to "yes – for longer than 3 months"). In scoring this musculoskeletal symptom subscale, items relating to the Beighton Scoring System (below) were omitted for group comparisons between hypermobile and non-hypermobile participants as hypermobile participants would naturally score higher. This represented a minor departure from the original scoring (in Iodice, 2013).

The 9-item Beighton Scoring System (Beighton et al., 1973) was followed by trained clinicians using objective measurements to assess participants' joint laxity. Scores of ≥4 were indicative of generalized joint laxity (GJL, also hereon referred to as "hypermobility") in-line with existing prevalence data (Clinch et al., 2011).

Clinical notes of participants were audited to determine clinical diagnosis of psychiatric or neurodevelopmental condition.

2.3 | Data preparation for statistical analyses

Chi-square tests were used to test for group differences in the proportion of people with GJL (i.e., a Beighton score of ≥4) between the participants and the comparison group. The expected frequencies were tested to ensure that the use of Pearson's chi-square was appropriate. Binary logistic regression was used to calculate the odds ratios of having GJL for participants compared to the general population comparison group. Differences between sexes in relation to GJL were also tested using chi-square tests in (a) participants and (b) the comparison group. Binary logistic regression was used to calculate odds ratios in relation to the likelihood of having generalized joint laxity across sexes within (a) participants and (b) the comparison group.

Chi-square tests were also used to ascertain if the proportion of individuals with GJL and a specific mental health disorder or neurodevelopmental condition differed between the two groups. Binary logistic regression was then used to calculate odds ratios denoting the likelihood of having GJL if an individual had a specific mental health disorder or neurodevelopmental condition.

The autonomic symptom data were assessed for normality, and given that data were non-parametric, Mann–Whitney *U* tests were used to examine quantitative differences in AQQoL symptom subscale scores between participants with and without GJL.

Factorial analyses of variance (ANOVAs) were used to test for interaction effects between GJL, sex, and AQQoL symptom subscale scores. Where symptom subscale scores did not follow a normal distribution (e.g., being positively skewed), these were transformed using a square root transformation prior to factorial ANOVA completion (Manikandan, 2010).

To investigate whether autonomic symptoms mediated the relationship between hypermobility and anxiety diagnosis, an estimation of indirect effects was performed using PROCESS macro v3.5 by Hayes (2017) within SPSS. The 95% bootstrapped confidence interval (CI) for the indirect effect is based on 1,000 samples and considered significant if the bootstrapped CIs do not cross zero. For this analysis, the outcome variable was anxiety diagnosis, the predictor variable was hypermobility (presence of GJL), and the mediator variable was orthostatic intolerance symptoms score.

TABLE 1 Demographic data on participating groups

Characteristics	Participants with a mental health disorder and/or neurodevelopmental condition ($n = 377$)	ALSPAC group representing general adolescent population ($n = 6{,}022$)
Age in years (*M*, *SD*)	38.9 (11.9)	13.8 (NR)
Sex, female (% of group)	196 (52%)	3,061 (51%)

Abbreviations: ALSPAC, Avon Longitudinal Study of Parents and Children; *M*, mean; NR, not reported.

TABLE 2 Most common diagnoses of mental health disorders and neurodevelopmental conditions

Diagnosis	*n* (%)
Anxiety	77 (20%)
Depression	129 (34%)
Bipolar affective disorder	66 (18%)
Schizophrenia	38 (10%)
Personality disorder	46 (12%)
ADHD	60 (16%)
Other	59 (16%)

Note: Due to co-occurring conditions, percentages will not add to 100%.
Abbreviation: ADHD, attention deficit hyperactivity disorder.

3 | RESULTS

3.1 | Demographic information

3.1.1 | Group data

Three-hundred and seventy-seven participants with diagnoses of mental health disorders or neurodevelopmental conditions were included in the study. Prevalence data reported in the ALSPAC birth cohort study (Clinch et al., 2011) were used in the (adolescent) general population comparison group, representing 6,022 individuals for whom a Beighton score was available (which was collected outside of this study and the raw data were not included in our study). Table 1 shows demographic information for the patient participants and the ALSPAC general population data. There was no significant difference between the number of those assigned female at birth in the study population group and the ALSPAC group (respectively, 52% vs. 51%, $p = .662$).

3.1.2 | Findings in group with diagnoses of mental health disorders and neurodevelopmental conditions

Most commonly, patients had received a diagnosis of depression ($n = 129$, 34%). This was followed by anxiety ($n = 77$, 20%), bipolar affective disorder ($n = 66$, 18%), and a personality disorder ($n = 45$, 12%)—see Table 2.

Patients who used mental health services often received more than one diagnosis for co-occurring disorders. Most commonly, patients experienced anxiety and depression concurrently ($n = 39$). Thirteen patients also experienced anxiety in co-occurrence with other conditions, and 13 patients experienced depression in co-occurrence with other conditions—see Table S1.

3.2 | Generalized joint laxity (hypermobility)

Of individuals with mental health disorders or neurodevelopmental conditions, 142/377 scored ≥4 on the Beighton score; that is, 38% had GJL (hypermobility). In the general population (ALSPAC) comparison group, 1,156/6,022 scored 4 or more on the Beighton score; that is, 19% (Figure 1). There was a significant association between these groups as to whether participants had joint laxity or not $\chi^2(1) = 74.84$, $p < .001$. The odds ratio of having GJL was 2.54 times higher (95% CI: 2.05, 3.16) if individuals had diagnoses of mental health disorders and/or neurodevelopmental conditions compared to those in the general population (ALSPAC) sample.

As expected, being assigned female at birth was associated with GJL in both patients and the general population, $\chi^2(1) = 24.75$, $p < .001$, $\chi^2(1) = 286.37$, $p < .001$ respectively (Figure 2). The odds of patients having GJL were 2.96 times higher (95% CI: 1.91, 4.59) if they were assigned female at birth compared to assigned male at

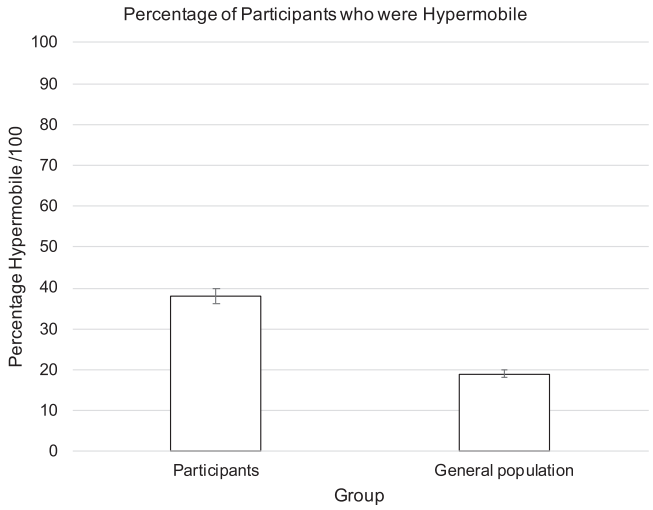

FIGURE 1 Percentage of individuals in each group who had generalized joint laxity. Error bars show 95% CI

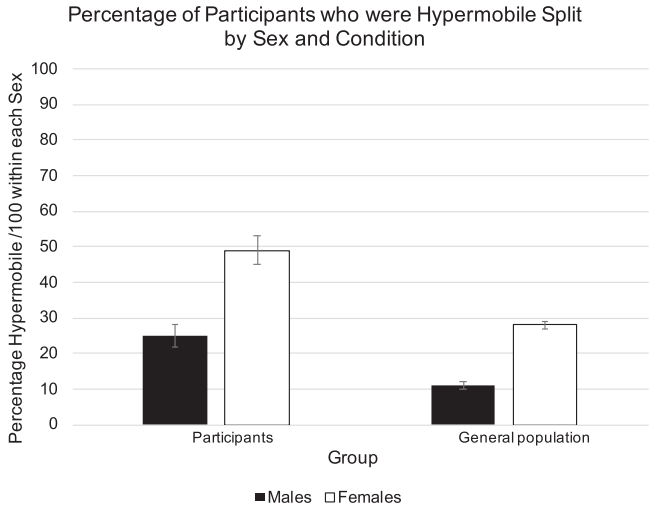

FIGURE 2 Percentage of participants who had generalized joint laxity within each sex across group. Error bars show 95% CI

birth. The odds of people in the general population having GJL were 3.2 times higher (95% CI: 2.78, 3.68) if they were assigned female at birth compared to assigned male at birth (Table 3).

3.3 | Mental health disorders, neurodevelopmental conditions, and GJL

Joint hypermobility was overrepresented in some mental health conditions more than others (i.e., anxiety, depression, and bipolar affective disorder $\chi^2[1] = 60.19$, $p < .001$, $\chi^2[1] = 66.27$, $p < .001$, $\chi^2[1] = 12.31$, $p < .001$—see Table 4). The odds of experiencing GJL compared to the general population was 5.05 times higher (95% CI: 3.21, 7.95) if someone had a diagnosis of anxiety, 3.9 times higher (95% CI: 1.26, 5.54) if someone had a diagnosis of depression and 2.4 times higher with a diagnosis of bipolar affective disorder (95% CI: 1.45, 3.99).

3.4 | Relationships between autonomic symptoms and GJL

Within the participant group with mental health disorders or neurodevelopmental conditions, some AQQoL symptom subscale scores were significantly higher in individuals with GJL compared to those without GJL ($p < .005$, see Table 1). These specifically included orthostatic intolerance score ($p = .006$), gastrointestinal symptom score ($p = .009$), and total symptom score ($p = .002$) (Figure 3, Table 5).

3.4.1 | Impact of sex and GJL on autonomic symptoms

Overall, there was a significant main effect of sex on each type of autonomic symptom subscale tested (Table 6). These indicated that those assigned female at birth had significantly higher total symptom scores (Figure 4), autonomic symptom scores, orthostatic intolerance scores, and gastrointestinal scores compared to those assigned male at birth.

3.4.2 | Mediation of relationship between hypermobility and anxiety by orthostatic intolerance

There was a significant indirect effect of hypermobility on anxiety diagnosis through orthostatic intolerance symptoms score, $b = .1302$, BCa CI [0.0245, 0.2701] (Figure 5), indicating that such dysautonomia mediates the relationship between joint hypermobility and anxiety.

4 | DISCUSSION

To our knowledge, this is the first study to investigate symptomatic autonomic dysfunction in connection with variant connective tissue (represented by GJL) in people accessing mental health services with diagnoses of mental health disorders or neurodevelopmental conditions. Significantly more patients with mental health disorders and/or neurodevelopmental conditions experienced GJL compared to the general population (here represented by a younger cohort), and GJL was significantly more likely to be experienced in those assigned female at birth. Overall, as hypothesized, autonomic dysfunction was significantly more prevalent in patient participants with GJL compared to those without GJL. Those assigned female at birth were shown to display significantly more autonomic symptoms compared to those assigned male, irrespective of having GJL, and these sex differences in symptoms warrant further exploration in the future. Our findings indicate that autonomic dysfunction (as demonstrated by symptoms of

TABLE 3 Demographics of patient participants split by hypermobility

Characteristics	Hypermobile participants ($n = 142$)	Non-hypermobile participants ($n = 235$)
Age in years (*M*, *SD*)	35.03 (10.98)	41.23 (11.8)
Sex, female (% of group)	97 (68.3%)	99 (42.1%)
Beighton score/9 (*M*, *SD*)	5.74 (1.68)	0.9 (1.08)

Abbreviation: *M*, mean.

TABLE 4 Association between GJL and mental health disorders and neurodevelopmental conditions

							95% CI	
	Hypermobile (*n*, %)	Non-hypermobile (*n*, %)	Chi-square	*df*	*p*	Odds ratio	Lower	Upper
Anxiety	42 (54.5%)	35 (45.5%)	60.19	1	<.001*	5.05	3.21	7.95
Depression	62 (48%)	67 (52%)	66.27	1	<.001*	3.90	1.26	5.54
Bipolar affective disorder	24 (36%)	42 (64%)	12.31	1	<.001*	2.41	1.45	3.99
Schizophrenia	2 (5%)	36 (95%)	4.74	1	<.029*	0.234	0.06	0.97
ADHD	28 (47%)	32 (53%)	28.60	1	<.001*	3.68	2.21	6.14
Personality disorder	13 (28%)	33 (72%)	2.67	1	.101	1.71	0.90	3.27

Note: Percentage is calculated within diagnosis category.
Abbreviations: ADHD, attention deficit hyperactivity disorder; CI, confidence interval; GJL, generalized joint laxity.
*$p \leq 0.05$.

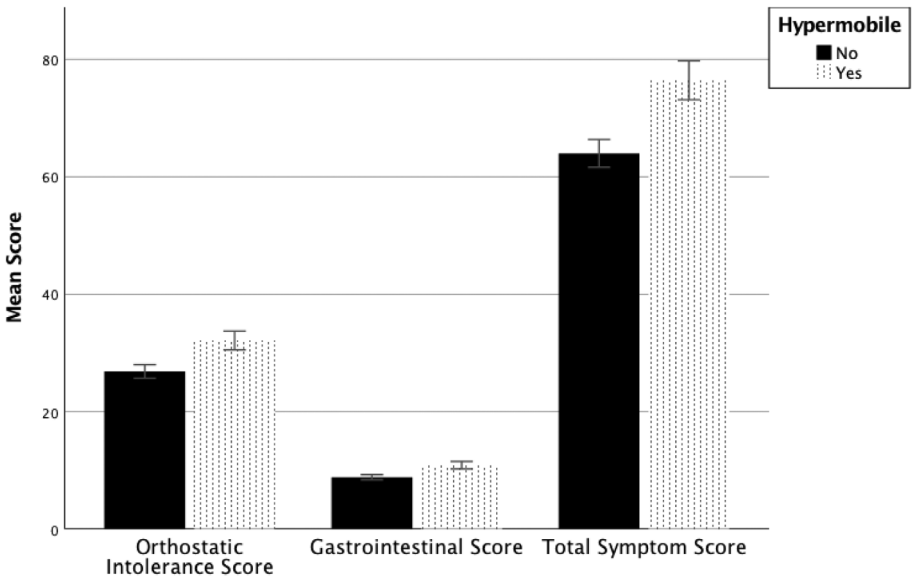

FIGURE 3 Graph shows the mean symptom scores measured using the Autonomic Questionnaire and Quality of Life Score (AQQoL) split by hypermobility. Error bars show ±1 *SEM*

orthostatic intolerance) mediate the relationship between hypermobility and anxiety status in this group.

In people accessing mental health services with diagnosed mental health disorders or neurodevelopmental conditions, 38% had GJL compared to 19% of the general population sample (i.e., the odds ratio of GJL was 2.54 higher if individuals were a patient). GJL was particularly likely in people diagnosed with anxiety and/or depression (approximately twice as likely compared to not having either of these diagnoses). These findings replicate previous research, demonstrating that people with hypermobility are significantly more likely to experience anxiety (Bulbena et al., 2011; Bulbena et al., 2017; Smith et al., 2014) and, to a lesser extent, depression (Smith et al., 2014). Although an association between hypermobility and bipolar affective disorder has been described in a population registry (Cederlöf et al., 2016), this is the first clinical study to show over-representation of hypermobility in those with bipolar affective disorder.

These findings underline the importance of clinical services in considering both physical and psychological health in combination (Bulbena et al., 2017), not least because people with symptomatic hypermobility are at increased likelihood of experiencing pain and multi-systemic challenges in addition to mental health difficulties. Hypermobility may explain why some people may be at increased risk

TABLE 5 Differences in symptom scores between individuals with and without generalized joint laxity (Mann–Whitney *U* tests)

	Mean (*SD*), median for hypermobile participants	Mean (*SD*), median for non-hypermobile participants	*U*	*z*	*p*	*r*
OI/120	31.96 (18.96), 31	26.85 (17.65), 24	19,309.5	2.77	.006*	0.14
GI/36	10.86 (7.51), 10	8.83 (6.72), 7	19,033.5	2.63	.009*	0.14
Bladder/28	4.52 (5.39), 3	5.54 (5.28), 4	14,137.5	−2.36	.018*	−0.12
Secretomotor/16	3.24 (2.69), 3	2.97 (2.53), 3	17,283.5	0.791	.429	
Sudomotor/44	10.17 (10.34), 7	9.89 (9.51), 7	16,392	−0.104	.917	
Autonomic subscale score/249	62.81 (36.3), 57.5	56.2 (33.54), 51.5	18,202	1.801	.072	
MSK symptom score/14	7.87 (3.99), 7	6.89 (4.37), 6	18,962.5	2.43	.015*	0.13
Total score/272	76.44 (39.18), 71	36.99 (36.15), 59.5	19,500.5	3.08	.002*	0.16

Abbreviations: GI, gastrointestinal; MSK, musculoskeletal; OI, orthostatic intolerance; *r*, effect size measure.
*Shows when $p < .05$.

TABLE 6 Differences in symptom scores between sexes and GJL status (ANOVAs)

	Variance across sexes and hypermobility status	Effect of sex on outcome	Effect of GJL on outcome	Interaction effect between sex and GJL
Total score	$F(3, 370) = 0.33$, $p = .802$	$F(1, 370) = 27.91$, $p < .001^*$, $r = 0.28$	$p > .05$	$p = .097$
Autonomic symptom score	$F(3, 370) = 0.05$, $p = .984$	$F(1, 370) = 27.34$, $p < .001^*$, $r = 0.26$	$p > .05$	$p > .05$
Orthostatic intolerance score	$F(3, 371) = 0.03$, $p = .994$	$F(1, 371) = 29.3$, $p < .001^*$, $r = 0.27$	$p > .05$	$p > .05$
Gastrointestinal score	$F(3, 370) = 2.21$, $p = .086$	$F(1, 370) = 25.44$, $p < .001^*$, $r = 0.26$	$p > .05$	$p > .05$
Bladder score	$F(3, 371) = 1.77$, $p = .152$	$F(1, 371) = 10.23$, $p = .002^*$	$F(1, 371) = 6.79$, $p = .010$	$p > .05$

Note: Where outcome scores were not normally distributed, these were transformed using a square root transformation prior to analysis. Where transformations did not reveal normal distributions, attention was paid to the Levene's test to ensure variances were equal.
Abbreviations: ANOVAs, analyses of variance; GJL, generalized joint laxity.
*Shows significant result ($p < .05$).

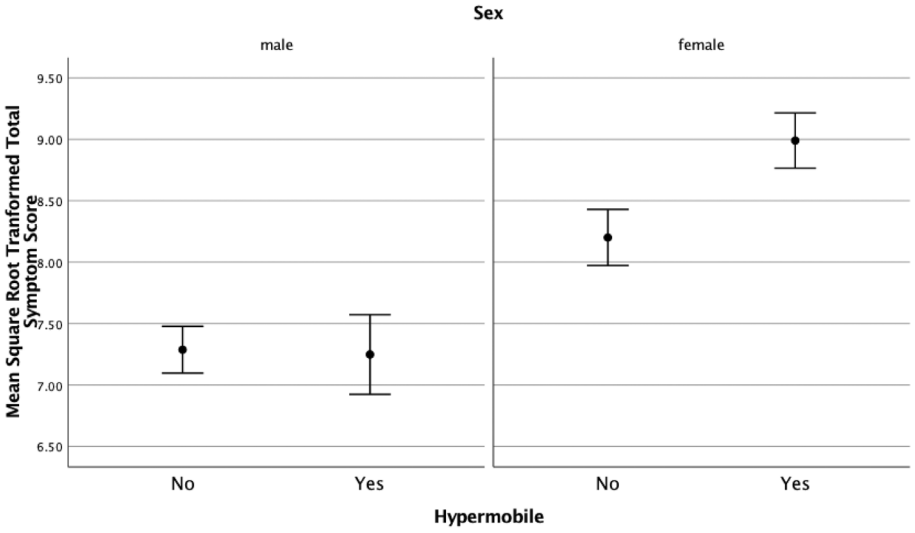

FIGURE 4 Graph shows the relationship between hypermobility and sex on square root transformed total symptom score. Error bars show ±1 *SEM*

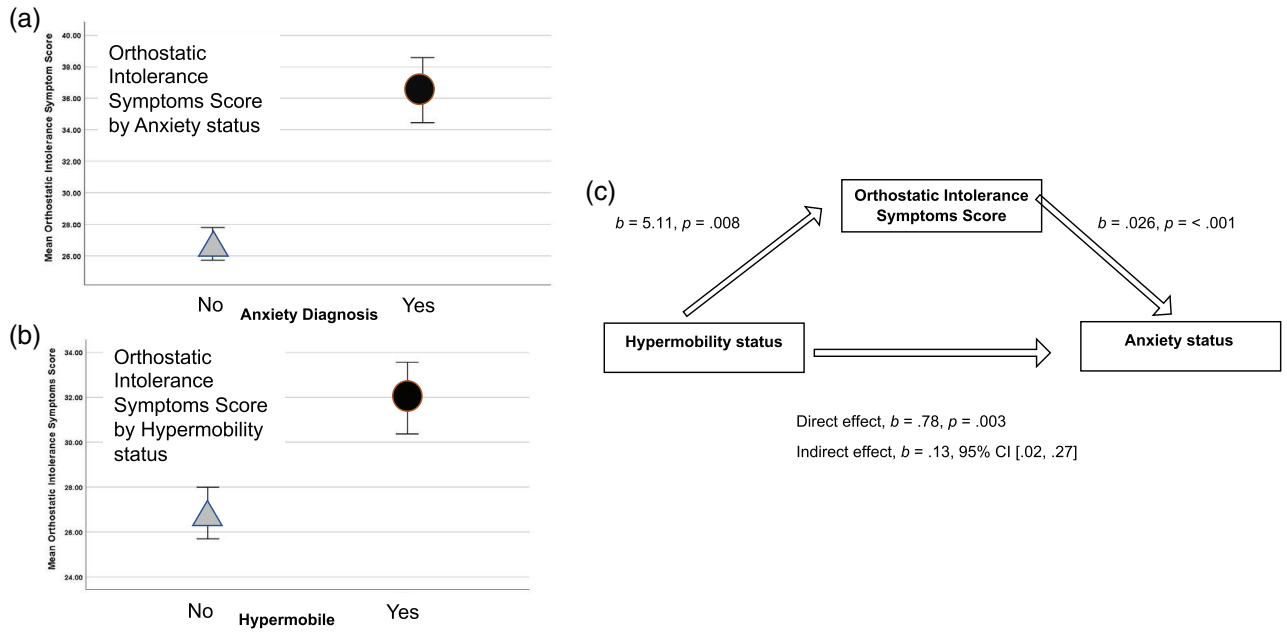

FIGURE 5 (a) Significant relationship between orthostatic intolerance symptoms and anxiety status. (b) Significant relationship between orthostatic intolerance symptoms (error bars = 1 *SEM*). (c) Model of hypermobility as a predictor of anxiety diagnosis, mediated by orthostatic intolerance symptoms. The confidence interval (CI) for the indirect effect is a BCa bootstrapped CI based on 1,000 samples

of developing anxiety disorders (Davies et al., 2021; Eccles et al., 2012; Eccles et al., 2015). We have demonstrated that this risk is mediated by autonomic dysfunction and is likely to represent a complex interplay of brain–body factors involving the influence of autonomic and interoceptive control on neural and emotional processing. These observations offer potential novel treatment targets (Davies et al., 2021; Quadt et al., 2021).

Therefore, screening for autonomic dysfunction and physical health problems in people with both mental health difficulties and GJL could be especially important in the context of the known increased likelihood of physical health problems in people with mental health problems generally, both to help improve overall health and associated morbidity (Liu et al., 2017; Osborn, 2001).

Our central hypothesis was supported; individuals with mental health disorders or neurodevelopmental conditions and GJL were more likely to report symptoms of autonomic dysfunction. This was shown to be particularly important in relation to symptoms of orthostatic intolerance, gastrointestinal, and musculoskeletal symptoms. Our findings extend previous observations in people with diagnosed symptomatic hypermobility (Celletti et al., 2017; Chan et al., 2019; Hakim & Grahame, 2004; Zarate et al., 2010), for whom orthostatic intolerance and gastrointestinal symptoms represent arguably the most common autonomic dysfunction difficulties (Dojcinovska, Cohen, & Wolman, 2019). This is crucial to consider due to the associated burden on quality of life (Fikree et al., 2017; Hakim et al., 2017) for individuals with GJL, and the potential impact of these symptoms on their mental health. For instance, orthostatic intolerance could lead people to experience anxiety related to possibly fainting in public. Syncope and PoTS have clear management guidelines and treatment and could substantially improve both patients' physical and mental health. Gastrointestinal difficulties could lead to increased symptoms of depression if people isolate themselves and avoid going out due to worries about how to manage these symptoms in public (Kopczyńska, Mokros, Pietras, & Małecka-Panas, 2018). Therefore, it is important to investigate the prevalence of such difficulties in combination with psychological and mental health challenges due to the need to develop an accurate holistic understanding of an individual's difficulties, to ensure that targeted and appropriate interventions are implemented.

The difference in sex in the groups with and without GJL is a possible limitation of this study which should be rectified in future research. Further exploration of the effect of medication on autonomic symptoms in such a group is warranted including formal autonomic function tests to explore the degree and severity of cardiovascular and sudomotor dysfunction. A further difficulty is the heterogenous nomenclature regarding hypermobility. This study quantified generalized joint laxity rather particular diagnoses of symptomatic hypermobility such as hEDS, and further work on the prevalence and role of hEDS in such multimorbidity is warranted, including the use of hEDS criteria variable Beighton cut-offs. It is important to consider that it is possible to have minimal joint symptoms and significant associated morbidity in other systems.

We have demonstrated that patients with mental health disorders and/or neurodevelopmental conditions have high rates of joint hypermobility and autonomic dysfunction, which in turn mediates the association between joint hypermobility and anxiety status in this group. Increased awareness and understanding of this process may enhance mechanistic understanding and targeted management of

multimorbidity, particularly co-occurring physical symptoms and mental health difficulties in the context of variant connective tissue.

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CONFLICTS OF INTEREST

No conflicts of interest.

AUTHOR CONTRIBUTIONS

The study was designed by Jessica A. Eccles and Hugo D. Critchley with assistance from Christopher J. Mathias and Valeria Iodice. Jenny L. L. Csecs and Jessica A. Eccles drafted the initial manuscript and conducted data analysis. Nicholas G. Dowell and Georgia K. Savage assisted with data analysis and visualization. All authors contributed to the drafting of the manuscript.

DATA AVAILABILITY STATEMENT

Anonymized datasets available on reasonable request to the corresponding author.

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